## REMARKS

Applicants respectfully request entry of this Preliminary Amendment prior to examination of the above-referenced case. This case is a continuation of parent Application No. 10/013,728, filed December 13, 2001, which is a continuation of grandparent Application No. 09/135,657, filed August 18, 1998. The present Preliminary Amendment is directed to the Final Office Action issu d in the parent case, Paper No. 9, mailed on March 12, 2003.

Claim 1 and new Claims 26 through 50 are pending in the application. Claims 2 through 25 were cancelled by an initial Preliminary Amendment submitted on September 11, 2003. Claims 26 through 50 have been added within the present Preliminary Amendment to complete the record for examination and highlight advantageous aspects of the invention.

Support for Claims 26 through 50 can be found in the application as filed. Claims 26 through 34 of the instant application correlate to Claims 27 through 35 in the parent application. Claim 36 of the instant application correlates to Claim 36 in the parent application. Claims 38 through 47 of the instant application correlate to Claims 38 through 47 in the parent application. Claims 48 and 49 of the instant application correlate to Claim 51 in the parent application. Similarly, Claim 26 through 37 of the instant application correlate to Claims 2 through 13 in the grandparent application, and Claims 38 through 49 of the instant application correlate to Claims 15 through 25 in the grandparent application.

Reexamination and reconsideration of this application, withdrawal of all rejections, and formal notification of the allowability of the pending claims are earnestly solicited in light of the remarks which follow.

Rejection Under 35 USC § 112

Claims 42 through 45 of the parent application stood rejected under 35 USC § 112.

Claim 42 of the present application (which, as noted above, correlates to Claim 42 of the parent application) has been amended to more clearly recite that aromatic hydrocarbons or alcohols may optionally be present within the physiologically tolerable solvent, as suggested by the Examiner.

Claim 45 of the present application (which, as noted above, correlates to Claim 45 of the parent application) has been amended to reflect more conventional United States practice regarding (a) the term "based on" as used in conjunction with plasticizers that include phthalate or camphor and (b) the term "derivatives" as used in conjunction with lanolin. Applicants nevertheless respectfully reiterate that one skilled in the art, such as a formulations chemist, would have been readily apprised of the meaning of the terms "phthalate-based plasticizer," "camphor-based plasticizer" and "lanolin derivatives."

Rejection Under 35 USC § 103

Claims 26, 27, 29 through 36, 38 and 40 through 54 within the parent application stood rejected under 35 USC § 103(a) as unpatentable over United States Patent No. 4,250,164 to Bernstein in combination with United States Patent No. 5,264,206 to Bohn et al. Claims 26 through 36, 38 and 40 through 54 of the parent application stood rejected under 35 USC § 103(a) as unpatentable over the combination of Bernstein and Bohn, and further in view of United States Patent No. 3,966,924 to Fredriksson. Claims 26, 27 and 29 through 54 of the parent application stood rejected under 35 USC § 103(a) as unpatentable over the combination of Bernstein and Bohn, and further in view of either United States Patent No. 5,120,530 to Ferro et al. or WO 96/14048 to Seidenschnur.

It may be useful to consider the invention as recited in the claims before addressing the merits of the rejection. The claims recite nail polish comprising one or more glucocorticoids, one or more physiologically tolerable solvents and one or more water-insoluble film-forming agents, which forms a stable nail polish.

In advantageous embodiments, the glucocorticoid may be selected from alclometasone dipropionate, amcinonide, beclomethasone dipropionate, bendacort, betamethasone benzoate, betamethasone dipropionate, betamethasone valerate, budesonide, clobetasol propionate, clobetasone butyrate, desonide, desoximetasone, dexamethasone, dichlorisone, diflorasone diacetate, diflucortolone valerate, difluprednate, fluazacort, flucinolone acetonide, fluclorolone acetonide, fludroxycortide, flumethasone pivalate, fluocinolone acetonide, fluocinonide, fluocortolone, fluorometholone, flupamesone, fluprednidene, fluprednidene acetate, flurandrenolide, halcinonide, halmetasone, hydrocortamate, hydrocortisone butyrate, methylprednisolone aceponate, mometasone furoate, prednicarbate, prednisolone, prednisone, tixocortol, or triamcinolone acetonide, as recited in Claim 26. In particularly advantageous embodiments, the glucocorticoid is clobetasol propionate, as recited in Claim 50. The glucocorticoids may beneficially be present in the nail polish in a total concentration of 0.5 % to 20 % by weight, as recited in Claim 28.

The lacquers of the invention may be formed from exemplary water-insoluble film-forming agents that include cellulose derivatives, such as recited in Claims 33 and 34, as well as poly(vinyl acetate); partially hydrolyzed poly(vinyl acetate); copolymers of vinyl acetate with acrylic acid or crotonic acid or monoalkyl maleate; ternary polymers of vinyl acetate with crotonic acid and vinyl neodecanoate; ternary polymers of vinyl acetate with crotonic acid and vinyl propionate; copolymers of methyl ethyl vinyl ether and monoalkyl maleates; copolymers of fatty acid vinyl esters and acrylic acid or methacrylic acid; copolymers of N-vinylpyrrolidone, methacrylic acid, and alkyl methacrylates; copolymers of acrylic acid and methacrylic acid, alkyl acrylates, or alkyl methacrylates, as recited in Claim 36. Exemplary water-insoluble film-forming agents further

include polymers, copolymers, or mixtures of one or more of ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride, polyvinyl acetals, polyvinyl butyrals, alkyl-substituted poly-N-vinylpyrrolidone, alkyl esters of copolymers of olefins and maleic anhydride, reaction products of colophony with acrylic acid, and benzoins, as recited in Claim 38.

Exemplary physiologically tolerable solvents include hydrocarbons, halogenated hydrocarbons, alcohols, ethers, ketones, esters, and mixtures thereof, as recited in Claim 40.

In further advantageous embodiments, nail lacquers in accordance with the invention may contain further additives, including substances having keratolytic activity and/or keratoplastic activity, as recited in Claims 45 and 47.

The transdermal delivery of drugs is generally considered to be problematic for a number of reasons. Several of the most significant issues associated with transdermal drug delivery relate to mass transport. During transdermal administration, a drug typically initially diffuses out of a drug reservoir or the like on its way to a particular transdermal delivery site on the patient, such as skin or nail tissue. The configuration of the drug reservoir impacts the drug's ability to diffuse out to the delivery site. Mass transport through a solid drug reservoir is generally considered more difficult than diffusion through a liquid reservoir, for example. Upon arriving at the delivery site, the drug subsequently diffuses through an application surface, more specifically diffusing through a keratin layer, prior to entering the bloodstream. The thicker the keratin layer, e.g. nail tissue, the more difficult the mass transport. The diffusional challenges encountered by potential drugs are further exacerbated by increases in the molecular weight of the drug. As a result, commercially successful transdermal delivery systems to date have typically employed smaller molecules within a liquid drug reservoir applied to a patient's skin.

In addition to mass transport challenges, transdermal delivery systems must also provide an adequate shelf life. Transdermal systems may be stored after manufacture for days or even months prior to sale. Hence the transdermal delivery systems must be stable over time. Transdermal

systems providing insufficient shelf life would be expected to deliver either inadequate or otherwise non-uniform amounts of drugs.

Based on the numerous difficulties associated with the transdermal delivery of drugs, only 7 compounds have been successfully administered transdermally on a commercial basis. And each of these 7 compounds has been delivered through the skin, a much thinner keratin layer in comparison to nails.

Surprisingly, Applicants have found that glucocorticoids can be incorporated into stable nail polish (also commonly referred to as lacquer) formulations, and that such nail polish or lacquer formulations could be subsequently used to transdermally deliver glucocorticoids from a solidified, water-insoluble film through a patient's nails to provide a therapeutic dose of the drug to the underlying nail bed. The treatment of psoriasis of the nails is known to be extremely difficult. Consequently, unpleasant treatment methods have commonly been heretofore employed in the treatment of psoriasis of the nails. Intralesional injections have been used to get steroids to penetrate the proximal nail fold area, for example. It is altogether unexpected that glucocorticoids, which are bulky, rigid cyclopentanoperhydrophenanthrene four-ring systems, can diffuse through, i.e. are bioavailable from, the solidified water-insoluble resins of the invention, and furthermore that the glucocorticoids then proceed to diffuse through a patient's nails.

Applicants respectfully submit that the claimed invention is patentable in light of Bernstein. Bernstein is generally directed to mixtures of topical steroid precursors, such as Valisone® from Schering Corporation and Cordran® from Dista Products Company, with commercially available nail polishes, such Revlon clear nail polish. (Col. 2, lines 6 – 11; Col. 1, lines 47 - 50 and Col. 1, line 65 - Col. 2, line 5) Bernstein's preferred topical steroid is a 0.1% lotion containing betamethasone valerate in an isopropyl alcohol/water mixture, commercially available as Valisone® lotion. (Col. 1, lines 53 – 63). Dr. Bohn's experiment was directed to mixtures that incorporating Bernstein's preferred lotion within clear nail polish. (The Examiner's attention is kindly directed to Dr. Bohn's Declaration, Paragraphs 6 and 7). In addition to lotions, Bernstein further notes mixtures

incorporating alternative topical steroid preparations, such as creams and ointments. Such creams and ointments are similarly noted to contain a small fraction of active pharmaceutical ingredient ("API"), such as from 0.01 to 0.1%, presumably within a carrier. (Col. 1, lines 50 – 53, noting reduced strength creams incorporating 0.01% active ingredient, as well as creams, ointments and lotions incorporating 0.1% active ingredient). Bernstein is silent as to a recommended range of steroid concentration within his polishes, other than a brief reference to a "50:50" mixture of topical steroid (preferably 0.1% Valisone® lotion) and nail polish (containing 0% API). (Col. 2, lines 6 – 12). Bernstein thus includes about 0.05 weight percent API, or less, within his polish formulation, as determined from the working examples. (Col. 2, lines 19 – 21, noting a 50:50 mixture of Valisone® lotion containing 0.1% API with nail polish containing 0% API for Examples 1 – 3 and Col. 2, lines 40 – 46 noting a 50:50 mixture of Cordran® lotion containing 0.05% API with nail polish containing 0% API ).

Bernstein, considered either alone or in combination with the art, does not teach or suggest the claimed invention. As noted above, it is surprising that the present nail polishes are stable compositions, as recited in the claims. Applicants respectfully submit that, in contrast to the opinion urged within the Office Action of the parent application, the formulations provided in Bernstein are not stable. For the Examiner's convenience, the Declaration by Dr. Bohn and associated exhibit (marked Exhibit I) submitted in the parent application have been enclosed herewith. As shown in Dr. Bohn's Exhibit I, Bernstein's formulations are extremely unstable, yielding precipitates within 45 seconds after their initial combination. Such precipitates were formed despite the great care taken in combining the two components, i.e. a layer of the Valisone® lotion was carefully superimposed on top of the Revlon clear nail polish and vice versa. The speed at which precipitates were formed despite the care taken in forming these formulations emphasizes the highly unstable nature of Bernstein's mixtures.

By way of background, Bottle Nos. 1 and 2 shown in the first page of Exhibit I contain Valisone® lotion prepared in accordance with Bernstein, as noted during the prosecution of the parent application. Such Valisone® lotions do not represent Bernstein's invention, however, they

are merely a precursor composition used as a means of incorporating active ingredient into nail polish. Bottles Nos. 3 and 4 shown in the first page of Exhibit I contain Revlon nail polish alone. (The Examiner's attention is kindly directed to Dr. Bohn's Declaration, Paragraph 6).

Dr. Bohn subsequently carefully poured, i.e. superimposed, an aliquot of Revlon nail polish on top of the Valisone® lotion in Bottle No. 2 and an aliquot of the Valisone® lotion on top of the Revlon nail polish in Bottle No. 3, in an attempt to produce initial formulations that include individualized component layers. Bottle 1 remains in the Exhibit as a control, indicating the stability of virgin Valisone® lotion over time. Bottle 4 similarly remains in the Exhibit as a control, indicating the stability of the virgin Revlon nail polish over time. (The Examiner's attention is kindly directed to Dr. Bohn's Declaration, paragraph 7).

After superimposing the Valisone® and Revlon nail polish (in Bottle Nos. 2 and 3 only), Dr. Bohn photographed the controls and formulations over time. Page 2 of Exhibit I indicates the stability of the same set of formulations and controls 45 seconds after superimposing the component layers. Page 3 of Exhibit I indicates the stability of the same set of formulations and controls 4 minutes after superimposing the component layers. Page 4 of Exhibit I indicates the stability of the same set of formulations and controls 7 minutes after superimposing the component layers. Page 5 of Exhibit I indicates the stability of the same set of formulations and controls 15 minutes after superimposing the layers. The superimposed layered arrangement within Bottles 2 and 3 was then disturbed to induce more intimate contact between the two components, and Page 6 of Exhibit I indicates the stability of the same set of formulations and controls 2 minutes after mixing and shaking. Page 7 of Exhibit I indicates the stability of the same set of formulations and controls 1.5 hours after mixing and shaking. Page 8 of Exhibit I indicates the stability of the same set of formulations and controls 20 hours after mixing and shaking. Page 9 of Exhibit I indicates the results after the same set of precipitated formulations and controls shown on Page 8 of Exhibit I were shaken again in an unsuccessful attempt to dissolve the precipitants/clots within Bottles 2 and 3.

As shown in Exhibit I, the control mixtures, i.e. the Valisone® and Revlon nail polish (in Bottles 1 and 4, respectively) remained stable. In contrast, bottles containing a combination of the two controls in accordance with Bernstein (i.e. Bottles 2 and 3) quickly became unstable. More specifically, Bottles 2 and 3 formed precipitants after only 45 seconds, and this instability worsened over time. In fact, clots had formed within both Botttles 2 and 3 only twenty hours after combining the Valisone® and Revlon nail polish, and these clots could not be dissolved by shaking. (The Examiner's attention is kindly directed to Dr. Bohn's Declaration, Paragraph 7).

Applicants would like to reiterate that the Valisone® and Revlon nail polish combinations were initially formed by merely superimposing one component over the other while taking care to avoid mixing, in an attempt to produce formulations having a layered arrangement of virgin components (such as shown on Pages 2 to 5 of Exhibit I). Hence Dr. Bohn's testing was designed to actually minimize the resulting precipitation by providing minimal initial contact between the two components of the formulation. Actual production/retail conditions would be expected to combine the components in a much more rigorous fashion, resulting in even more severe precipitation/clot formation, as demonstrated by the mixed and shaken samples in Bottles 2 and 3 on Pages 6 to 8 of Exhibit I. As noted above, this precipitation/clots would not dissolve with subsequent agitation, as demonstrated by the re-shaken Bottles 2 and 3 on Page 9 of Exhibit I.

Applicants respectfully submit that Dr. Bohn's Declaration and Exhibit I are clear and convincing evidence of the instability of Bernstein's compositions. Such instability is of tremendous practical significance, e.g. determinant of commercial success, and is statistically relevant.

The Office Action asserts that Bernstein's alternate topical steroid precursors would not contain water, and thus not be unstable. Applicants respectfully submit, however, that water would not necessarily be absent from Bernstein's alternative embodiments. (The Examiner's attention is kindly directed to MPEP § 2112, "The mere fact that that a certain thing may result from a given set of circumstances is not sufficient." *In re Roberston*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950 – 51 (Fed. Cir. 1999) and further "the examiner must provide a basis in fact and/or technical reasoning

to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the prior art" *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990)). More particularly, creams by definition always contain water, as well known to one skilled in the art. Aqueous creams employ water as the outer phase, while emollient creams include water within the inner phase.

Furthermore, Applicants respectfully submit that Bernstein's alternative formulations incorporating topical creams or ointments may not have been stable when mixed with commercially available nail polish, regardless of the presence of water, depending on the exact composition of the cream or ointment. Bernstein is unfortunately silent as to the details of the remaining components within the topical steroid creams and ointments used in his alternative embodiments. The only specific precursor composition noted by Bernstein, the composition of the lotion, was found to be highly unstable.

Consequently, Applicants respectfully submit that Bernstein, considered either alone or in combination with the art of record, does not teach or suggest the claimed invention, reciting nail polishes formed from one or more glucocorticoids, one or more physiologically tolerable solvents and one or more water-insoluble film-forming agents, which forms a stable nail polish. As noted by the Examiner, Bernstein further does not teach or suggest the numerous advantageous glucocorticoids recited in Claim 26 or 27. The combination most certainly does not teach or suggest the highly advantageous glucocorticoid, clobetasol propionate, recited in Claim 50. In fact, Bernstein teaches away from the use of clobetasol propionate, a super high potency corticosteroid, by incorporating much less potent corticosteroids, i.e. the topical preparations Valisone® and Cordran®, into his formulations.

Nor does Bernstein teach or suggest the presence of such glucocorticoids in the beneficial amounts recited in Claims 28, 29, 31 and 32. In fact, Bernstein teaches away from the beneficial concentrations of Claims 28, 29, 31 and 32 by employing much smaller amounts of active

ingredients within his polish formulations, e.g. by employing less than a tenth of the minimum amount recited in Claim 28.

Bernstein further does not teach or suggest the advantageous film-forming agents recited in Claim 36 through 39 or the beneficial physiologically tolerable solvents recited in Claims 40 through 44. Bernstein most certainly does not teach or suggest that the nail polish may advantageously contain further additives, such as substances having keratolytic or keratoplastic activity, as recited in Claims 45 through 47.

Accordingly, Applicants respectfully submit that Bernstein does not teach or suggest the claimed invention. Applicants thus further respectfully submit that the pending claims are patentable in light of Bernstein, considered either alone or in combination with the art of record, on this basis alone.

Applicants additionally respectfully submit that it is doubtful that Bernstein's formulations provide any beneficial clinical effect, and thus there would have been no reasonable expectation of success based on his teachings. As noted above, one of the primary challenges involved in the treatment of nail psoriasis is the transport of a sufficient amount of active ingredient to the affected area. Further, upon reaching the application site, different corticosteroids have been found to exhibit different potencies in the treatment of psoriasis. A ranking of the efficacies of various corticosteroids in treating psoriasis of the skin is attached as Exhibit II. As shown in Exhibit II, the clobetasol propionate recited in Claim 50 has been determined to have a super high potency rating in the treatment of psoriasis (Class I of VII, with I being most potent). In contrast, the Valisone® lotion recommended by Bernstein has been found to be much less effective in the treatment of psoriasis (Class V of VII).

The minimal amounts that Bernstein incorporates into his formulations, which Applicants hypothesize may have been due to the extreme instability of his mixtures, further exacerbates the ineffectiveness of the resulting nail lacquers. More particularly, Applicants submit that only a

minimal quantity of a lesser effectiv corticosteroid would have been delivered to the site, even if Bernstein's formulations were stable (which Applicants submit that they are not). Consequently, in addition to the myriad of distinguishing features noted above, Applicants further respectfully submit that there would have been no reasonable expectation of success, even if Applicants had looked to Bernstein (which they did not do), and therefore the claimed invention is patentable over Bernstein on this basis alone.

Applicants respectfully submit that the secondary reference does not cure the deficiencies within the primary reference. The '206 patent lists Dr. Bohn and Dr. Kraemer of the present invention as co-inventors. The '206 patent is directed to nail lacquers containing at least one water insoluble film-former and at least one antimycotic agent. (Col. 2, lines 58 – 63). Exemplary antimycotic agents include tioconazole and/or econazole. (Col. 4, lines 31 – 33). Exemplary water insoluble film-formers include polyvinyl acetate and the like. (Col. 2, line 61 – Col. 4, line 9). The '206 patent further notes exemplary lacquers for the treatment of mycotic nails that include a water insoluble film former and 1-hydroxy-2-pyridone. (Col. 2, lines 10 – 20 and Col. 4, lines 10 - 15).

Applicants respectfully submit that the '206 patent does not teach or suggest the claimed invention, reciting nail polishes formed from one or more glucocorticoids, one or more physiologically tolerable solvents and one or more water-insoluble film-forming agents, which forms a stable nail polish. Applicants respectfully note that the claimed invention is not merely directed to water-insoluble film forming agents per se. Rather, the claimed invention is directed to compositions that combine glucocorticoids with water-insoluble film-forming agents. The '206 patent teaches away from such a combination (which recites molecules much larger those employed in the '206 patent) by emphasizing the diffusional challenges associated with transdermal systems employing solidified drug reservoirs. ((Col. 2, lines 2 – 6) "[t]he success of this [conventional] formulation has presumably been unsatisfactory ... because of the lack of adequate bioavailability of the active substance ... after the lacquer has dried"). As noted above, diffusional challenges become increasing difficult for larger molecules, e.g. the recited glucocorticoids.

There would have been no motivation to have combined these references. Applicants respectfully note that merely because the references can be combined is not enough, there must still be a suggestion. MPEP 2143.01 (section citing Mills).

However, even if the cited references were combined (which Applicants submit should not be done), the claimed stable compositions would not result. Bernstein is directed to polish mixtures that include comparatively small amounts of active substance that are further incorporated into the polish as a topical steroid precursor. The '206 patent is directed to compositions formed from antimycotic agents and water insoluble film formers. As evidenced by Dr. Bohn's declaration and Exhibit I, Bernstein's topical steroid precursors are unstable when combined with the water insolubl film formers of the '206 patent.

Consequently, neither Bernstein or the '206 patent, considered either alone or in combination, teaches or suggests the recited stable nail polishes formed from one or more glucocorticoids, one or more physiologically tolerable solvents and one or more water-insoluble film-forming agents. The combination thus does not teach or suggest the numerous advantageous glucocorticoids recited in Claims 26 or 27. The combination most certainly does not teach or suggest the highly advantageous glucocorticoid, clobetasol propionate, recited in Claim 50.

The combination further does not teach or suggest glucocorticoids in the beneficial amounts recited in Claims 28, 29, 31 and 32. In fact, the combination of references teaches away from such beneficial concentrations by employing much smaller amounts within the primary reference.

Fredricksson is generally directed to ointments containing a combination of corticosteroid, particularly halogenated corticosteroid, and 5-fluorouracil to treat psoriasis. (Col. 2, lines 43 – 44 and Col. 1, lines 44 – 50). The corticosteroid is preferably present in amounts of up to 0.1 %. (Col. 4, lines 15 – 16). In contrast to the opinion urged in the Office Action, Applicants respectfully

reiterate that Fredricksson does not teach the equivalence of various corticosteroids. Rather, Fredricksson merely provides a laundry list of exemplary corticosteroids which may be incorporated into topical compositions.

Consequently, Fredricksson, considered either alone or in combination with the art of record, does not teach or suggest the recited stable nail polishes, much less such polishes formed from one or more physiologically tolerable solvents and one or more water-insoluble film-forming agents. The combination further does not teach or suggest the numerous advantageous glucocorticoids recited in Claims 26, 27 and 50. Fredricksson thus most certainly does not teach or suggest such stable nail polishes incorporating glucocorticoids in the beneficial amounts recited in Claims 28, 29, 31 and 32. Fredricksson further does not teach or suggest the advantageous film-forming agents recited in Claim 36 through 39 or the beneficial physiologically tolerable solvents recited in Claims 40 through 44. Fredricksson also does not teach or suggest that the recited nail polish may advantageously contain further additives, such as substances having keratolytic or keratoplastic activity, as recited in Claims 45 through 47.

Again, there would have been no motivation to have combined these references. However, even if the cited references were combined (which Applicants submit should not be done), the claimed stable compositions would not result. Bernstein is directed to polish mixtures that include comparatively small amounts of active substance that are further incorporated into the polish as a topical steroid precursor. Fredricksson is directed to topical ointments. The '206 patent is directed to compositions formed from antimycotic agents and water insoluble film formers. As evidenced by Dr. Bohn's declaration and Exhibit I, Bernstein's or Fredricksson's topical steroid precursors would be expected to be unstable when combined with the water insoluble film formers of the '206 patent. Consequently, the combination of references does not teach or suggest the recited nail polish comprising one or more glucocorticoids, one or more physiologically tolerable solvents and one or more water-insoluble film-forming agents, which forms a stable nail polish.

Ferro is directed to nail varnishes containing an antimycotically-active substance and water-insoluble film former having a low content of quaternary ammonium groups. (Col. 1, lines 22 – 25 and lines 35 – 40). The water-insoluble film former is noted to be a copolymerizate of acrylic acid esters and methacrylic acid esters. (Col. 1, lines 35 - 40). Ferro merely broadly notes that the copolyermizate may include both methyl methacrylate and ethyl acrylate. (Col. 3, lines 30 – 35).

Ferro, considered either alone or in combination with the art of record, does not teach or suggest the recited stable nail polishes formed from one or more glucocorticoids, one or more physiologically tolerable solvents and one or more water-insoluble film-forming agents. Ferro thus does not teach or suggest the advantageous range of film forming agents recited in Claim 38. And Ferro further most certainly does not teach the beneficial molar ratios ratios recited in Claim 39. Ferro also does not teach or suggest nail polishes incorporating the numerous advantageous glucocorticoids recited in Claims 26, 27 and 50. Nor does Ferro teach or suggest such stable nail polishes incorporating glucocorticoids in the beneficial amounts recited in Claims 28, 29, 31 and 32. Ferro further does not teach or suggest the claimed nail polishes incorporating the beneficial physiologically tolerable solvents recited in Claims 40 through 44. Ferro also does not teach or suggest that the recited nail polish may advantageously contain further additives, such as substances having keratolytic or keratoplastic activity, as recited in Claims 45 through 47.

Seidenschnur is directed to solvent systems used to form nail lacquers containing vitamin D metabolite or derivatives or vitamin A derivatives, both of which were known to be difficult to dissolve. (Page 2, lines 11 – 17 and Page 3, lines 5 – 6). Seidenschnur recommends methylene chloride as a preferred solvent for his nail lacquers, due to its superior ability to penetrate keratinic material. (Page 3, lines 11 – 12 and lines 20 - 21). Seidenschnur generally notes that the nail lacquer may be formed from an acrylic resin, particularly an acrylic resin based on acrylic acid esters and methacrylic acid esters. ( Page 3, lines 26 – 27 and Page 6, lines 28 – 32). Seidenschnur is silent, however, as to exemplary monomer ratios for use in his nail lacquers.

Seidenschnur, considered either alone or in combination with the art of record, does not teach or suggest the recited physiologically tolerable solvents of the claimed invention. In fact, by expressly noting methylene chloride as a preferred solvent, Seidenschnur actually teaches away from the claimed invention, and especially the beneficial physiologically tolerable solvents recited in Claims 40 through 44. Seidenschnur further does not teach or suggest the numerous advantageous glucocorticoids recited in Claims 26, 27 and 50 or the beneficial glucocorticoid amounts recited in Claims 28, 29, 31 and 32. Seidenschnur further does not teach or suggest the claimed nail polishes employing the advantageous film-forming agents recited in Claim 36 through 39. Seidenschnur also does not teach or suggest that the recited nail polish may advantageously contain further additives, such as substances having keratolytic or keratoplastic activity, as recited in Claims 45 through 47.

There would similarly have been no motivation to have combined these references. However, even if the cited references were combined (which Applicants submit should not be done), the claimed stable compositions containing physiologically tolerable solvents would not result. Bernstein is directed to polish mixtures that include comparatively small amounts of active substance that are further incorporated into the polish as a topical steroid precursor. The '206 patent is directed to compositions formed from antimycotic agents and water insoluble film formers. Ferro is directed to nail varnishes containing an antimycotically-active substance and water-insoluble film former having a low content of quaternary ammonium groups. Seidenschnur is generally directed to the use of methylene chloride in nail lacquer compositions. Consequently, the combination of references does not teach or suggest the recited nail polish comprising one or more glucocorticoids, one or more physiologically tolerable solvents and one or more water-insoluble film-forming agents, which forms a stable nail polish.

Based on the foregoing, Applicants respectfully submit that Claims 1 and 26 through 48 are patentable in light of the art of record, considered either alone or in combination.

## CONCLUSION

It is respectfully submitted that Applicants have made a significant and important contribution to the art, which is neither disclosed nor suggested in the art. It is believed that all of pending Claims 1 and 26 through 50 are now in condition for immediate allowance. It is requested that the Examiner telephone the undersigned if any questions remain to expedite examination of this application.

It is not believed that fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional fees are necessary to allow consideration of this paper, the fees are hereby authorized to be charged to Deposit Account No. 50-2193.

Respectfully submitted,

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## CERTIFICATE OF FACSIMILE TRANSMISSION

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